

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/23814>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

sex hormones was investigated in a genetic model of generalized absence epilepsy.

Forty-eight WAG/Rij rats served as subjects: 24 males and 24 females. At age 3 months, 12 males and 12 females were gonadectomized under anesthesia; the other 24, 12 in each group, were sham operated. At age 6 months, under anesthesia, all rats had EEG electrodes implanted. One week later, EEGs were recorded, and spike-wave discharges (SWD) were counted.

The four groups of WAG/Rij rats differed in the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of SWD. These EEG data confirm the view that circulating gonadal hormones are a controlling factor in the number of spontaneously occurring SWD. Furthermore, they indicate that testosterone may have antiabsence effects and that the female sex hormones may promote the occurrence of SWD. We suggest that the slightly less favorable prognosis for girls than for boys with absence epilepsy may be a result of the proconvulsant effects of female steroid hormones and the antiepileptic activity of testosterone.

**Effects of Intrathalamic Injections of Muscimol and Bicuculline on Spike-Wave Discharges and Frequency Spectra in Rats.** C. van Rijn, Sabine Gijzen, and E. L. J. M. van Luijtelaa (NICI/Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands).

$\gamma$ -Aminobutyric acid (GABA) is differentially involved in convulsive and nonconvulsive epilepsy: Peripheral administration of GABA agonists inhibits convulsions but facilitates spike-wave discharges. Intracerebroventricular injections with muscimol or THIP also facilitates spike-wave discharges (SWP). The lateral part of the thalamus is involved in the genesis of SWD, it receives and projects to the reticular thalamic nucleus, the pacemaker for EEG oscillations such as sleep spindles and SWD. We investigated the role of GABA in the ventroposterolateral nucleus (VPL) of the thalamus and the relation between the antiabsence effects and the spectral changes: Many antiepileptic drugs have a major effect on the spectral content of the EEG.

WAG/Rij rats were bilaterally implanted with cannulas in the VPL and with cortical EEG electrodes. Bilateral injections of solvent, 0.02 and 0.2 nmol/0.3  $\mu$ l muscimol, and 0.15 nmol/0.3  $\mu$ l bicuculline (BIC) were given alone or in combination. SWD and the spectral content of the cortical EEG were analyzed. Muscimol dose-dependently decreased the incidence and the number of SWD. After the higher dose, SWD were almost absent for 3 h. BIC slightly increased the duration of SWD and partly antagonized the effects of muscimol. Spectral analyses of the EEG showed a dose-dependent increase after muscimol in the delta band and a decrease in theta and beta power. BIC had no effect on the spectral content. Histological verification of the injection site confirmed that the cannulas were aimed at the VPL. Liu et al. (1991) also reported suppression in the most lateral part of the thalamus, including the reticular thalamic nucleus.

The significant dose-dependent suppression of the number and duration of SWD after muscimol administration may suggest that the membranes of thalamic relay cells become depolarized through GABAergic activation—probably of interneurons. This might prevent the occurrence of EEG oscillations. The dose-dependent changes in the frequency spectra were not antagonized by BIC, suggesting that different factors are involved in the suppressive effects of SWD and the changes in the EEG spectrum.

**Endogenous Amino Acid Neurotransmitters in the Brains of Rats With and Without Spike-Wave Discharges.** C. M. Van Rijn, A. Van Raay-Selten, E. Willems, R. Wevers, and E. L. J. M. Van Luijtelaa (Departments of Psychology/NICI and Anaesthesiology, University of Nijmegen, Nijmegen, The Netherlands).

WAG/Rij rats are regarded as a genetic model for human absence epilepsy because as they spontaneously show spike-

wave discharges (SWD) in the EEG. An imbalance between excitation and inhibition may underlie the pathogenesis of SWD. We determined concentrations of several amino acid neurotransmitters in five brain regions in two strains of animals: WAG/Rij rats and ACI rats. The latter animals do not have SWD.

After rats were decapitated, the brains were removed (each strain  $n = 10$ ). The hippocampus, striatum, mesencephalon, thalamus, and frontal cortex were dissected. The parts were homogenized. The total homogenate was analyzed by chromatography with an amino acid analyzer. Data were evaluated by analysis of variance.

All the amino acids determined showed regional concentration differences. Strain differences were also noted: in all areas tested, asparagine, glutamine, and glycine concentrations were lower in the WAG/Rij than in the ACI animals. Higher concentrations of taurine were present in the WAG/Rij than in the ACI strain, but only in the hippocampus and in the frontal cortex. No strain differences were noted in glutamic acid, serine, or  $\gamma$ -aminobutyric acid (GABA).

We suggest that excess inhibition mediated by GABA underlies the genesis of the SWD. However, the GABA content was not different in the two strains. The concentrations of amino acids that modulate excitation (including glycine) were lower in the WAG/Rij rats than in the ACI rats. The role of taurine in epileptogenesis is still unclear. Future research must clarify whether the observed differences are due to strain differences, are the cause of SWD, or are a secondary consequence of SWD. Nevertheless, our results show that the debate over the inhibition–excitation imbalance is not yet settled.

**Can Polyunsaturated Fatty Acids Exert an Antiepileptic Effect In Vivo?** R. A. Voskuyl, K. B. Postel-Westra, A. Cleton, and A. Leaf (Department of Physiology, Leiden, The Netherlands).

Recent evidence indicates that polyunsaturated fatty acids (PUFAs) derived from fish oil, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can prevent lethal ischemia-induced cardiac arrhythmias in animals and possibly also in humans. In isolated cardiac myocytes, EPA and other PUFAs decreased the excitability (i.e., increased action potential threshold and increased refractory period). The decreased excitability can be explained by the voltage-dependent decrease in sodium current and the shift in steady-state inactivation curve in a hyperpolarizing direction that has been demonstrated in these cells. If PUFAs had the same effect on central neurons, these compounds might be expected to exert an anticonvulsant effect. Several antiepileptic drugs have been shown to affect sodium currents, an action that may contribute to their anticonvulsant effect. We tested this possibility in the cortical stimulation model. Chronic cortical stimulation electrodes for determination of the convulsive threshold and intravenous and intraarterial canulas for drug administration and blood sampling were implanted in rats. EPA or DHA was infused for 30 min, with albumin in physiological saline as carrier. EPA and DHA only moderately increased the threshold as compared with pretreatment baseline. After infusion, the threshold remained slightly increased for several hours and returned to baseline after 24 h. Vehicle alone did not affect the threshold.

The extent to which PUFAs affect sodium channels in isolated neurons is not known. Therefore, PUFAs may simply be less effective in the CNS than in heart cells. Alternatively, pharmacokinetic factors may have played a decisive role in our experiments and we may thus have failed to reach a sufficiently high free concentration in the brain to produce a clear antiepileptic effect. Further research is necessary to resolve these matters.

**Opposite Effects of Kindling Epileptogenesis and Carbamazepine on Sodium Currents in Rat Hippocampus CA1 Neurons.** M. Vreugdenhil and W. J. Wadman (Amsterdam, The Netherlands).

The whole-cell sodium current ( $I_{Na}$ ) and its modulation by carbamazepine (CBZ 15, 40, 100  $\mu$ M) was studied in hippocampal